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Private Citizen*

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Subject: PUBLIC COMMENT

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*Dr. Crosby is currently employed by AbbVie and is commenting in her personal capacity.

Below, I am providing my comments on the NTP Studies of Cell Phone Radiofrequency Radiation in Rats (TR-595) and in Mice (TR-596), which specifically address the genetic toxicology results and their potential relevance to carcinogenesis.

1) In TR-595, the Abstract indicates that the genetic toxicity evaluation was a part of the 2-year studies and that the comet assay and micronucleus test were performed after 14 weeks of exposure. However, in Table 1 of the Materials and Methods, genetic toxicology studies are not listed as a part of the experimental design, although there is a reference to an interim necropsy necropsy being "17 weeks" in this table. In the results for TR-595, Tables E1 – E9 indicate that the time point was 19 weeks.

   In Table 1, TR-596, "2-Year Studies," there is no mention of an interim necropsy under "Necropsy Dates." However, in this table, there is reference to a 14 week necropsy under "Necropsy."

   For both reports, the authors may consider reviewing the consistency of the sections and ensuring that the information pertaining to the genetic toxicology studies and their respective durations are clear.

2) In TR-595 and TR-596, the Materials and Methods sections indicate that the 28-day and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice (GLP) Regulations (21 CFR, Part 58). Were the genetic toxicology studies conducted under the same GLP regulations? Since the description of the Materials and Methods for the Genetic Toxicology studies follows the "Quality Assurance Methods" section, it is unclear to the reader as to whether similar QA methods were applied.

3) The Introduction indicates that the absorption of cell phone RFR is dependent on the frequency of the signal and the dielectric properties of the exposed tissue. Gabriel (2000) elaborates stating that RF pulse and amplitude duration, as well as the geometry/permittivity and conductance properties of the exposed tissue are important. Though some of this is mentioned in the section pertaining to the "Absorption of Cell Phone Radiation" together with the IARC, 2013 reference, there may be additional information included to help the reader consider

individual tissue specific absorption rate (SAR) values (as described in the literature). This may be helpful for contextualizing and/or supporting the results of TR-595 and TR-596 studies.

Gabriel C. (2000). The Dielectric Properties of Tissues. In: Klauenberg B.J., Miklavčič D. (eds) Radio Frequency Radiation Dosimetry and Its Relationship to the Biological Effects of Electromagnetic Fields. NATO Science Series (Series 3: High Technology), vol 82. Springer, Dordrecht

4) A result from the comet assay in the rats (TR-595) showed that there was a statistical significant increase in the percent tail DNA in the hippocampus cells of males that were exposed to CDMA-modulated cell phone RFR (100-cell method). With a P Value = 0.019 at the top dose (6 W/kg) this was the only clear positive from this study. This result was not found in females and did not occur in any rats exposed to GSM-modulated cell phone RFR. However, when counting 150 cells, the result in the CMDA-modulated cell phone RFR-exposed male rats was not replicated. Given the two methods for evaluating the data and given the lack of historical data provided, the authors may want to comment upon or note the variability in the sham control values for the individual tissues across the methods (i.e., male, rat, liver, CDMA, 100-cell method, sham control percent tail DNA = 13.81 ± 2.88; male, rat, liver, sham control percent tail DNA, CDMA, 150-cell method = 25.71 ± 8.71).

   Likewise, in TR-596 (mouse study) it noteworthy to see the differences in the male vs. female sham control percent tail DNA in the frontal cortex, where the male value of percent tail DNA was 0.63 ± 0.08 and the female value was 8.11 ± 2.13.

   Though the authors mention no appropriate historical control database to provide context for the response, the variation in the sham controls between evaluation methods (re: TR-595) and the sexes (re: TR-596) should be addressed.

5) The rationale for the tissue selection for the comet evaluation may also be something for discussion. Both studies (TR-595 and TR-596) employed robust histopathology evaluation. With the limited set of tissues evaluated in the comet assay, the potential for genetic toxicology to help in ruling in/out mechanistic insights may have been missed. The review of other tissues beyond those selected in the studies is/would have been desirable. (The authors also note that the tissues evaluated for genetic toxicology were not reviewed for histopathology; hence there may have been confounding information such as necrosis.)

6) Having listened to the webcast, several panelists discussed the scope and audience for the reports, mentioning that a glossary of terms could help readers familiarize themselves with language used in the document. Regarding this, the authors may consider discussing the meaning of ‘hazard assessment’ and ‘risk assessment’ as they are used in safety assessment. A statement of relevance, perhaps noting the studies overall outcomes and limitations could also be included.